International Immunopharmacology 27 (2015) 244–248

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Invited commentary

A novel use for testosterone to treat central sensitization of chronic pain in fibromyalgia patients

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ARTICLE INFO

Article history:
Received 2 March 2015
Received in revised form 27 April 2015
Accepted 11 May 2015
Available online 21 May 2015

Keywords:
Testosterone
Nociception
Fibromyalgia
Chronic pain
Central sensitization
Inflamed nociceptive nervous system
Stress

ABSTRACT

Fibromyalgia is a diffuse chronic pain condition that occurs predominantly in women and may be under-reported in men. Symptoms include a loss of feeling of well-being and generalized widespread flu-like muscle aches and pain that fail to resolve due to central sensitization of nociceptive neurons. It has commonalities with a myriad of other chronic pain conditions which include PTSD, "Gulf War Syndrome", and various stress-induced conditions caused, for example, by viral infection, emotional or physical stress, trauma, combat, accident or surgery. It is not understood why some individuals are susceptible to this condition and others are not. White et al., elsewhere in this issue, present a clinical feasibility study designed to test the hypothesis that 1) low or deficient testosterone serum levels are linked to a high risk for an inflamed nociceptive nervous system and resultant chronic pain states, and 2) a testosterone transdermal gel applied once a day by fibromyalgia patients can be an effective therapeutic against chronic pain. Here, a short profile of fibromyalgia is provided along with a brief summary of best practices currently recommended by clinical specialists. The link between testosterone and pain is then discussed, with an overview of scientific studies that lay the foundation for testosterone as a possible important additional therapeutic that has the potential to be safely administered and effective but also avoid the adverse effects of other therapeutics. Finally, novel mechanisms by which testosterone therapy is likely to down-modulate pain signaling are proposed.

Contents

Abbreviations: BBB, blood brain barrier; CNS, central nervous system; ENK, enkephalin; GABA, gamma-aminobutyric acid; HPA axis, hypothalamus, pituitary, adrenal endocrine axis; HPO axis, hypothalamus, pituitary, ovary endocrine axis; NSAID, nonsteroidal anti-inflammatory drug; OPIAD, opioid-induced androgen deficiency; PAG, periaqueductal gray neurons; RVM, rostral ventromedial medulla; SHBG, sex hormone binding globulin; SNRI, serotonin–norepinephrine reuptake inhibitor; SP, Substance P; SSRI, selective serotonin reuptake inhibitors.

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http://dx.doi.org/10.1016/j.intimp.2015.05.020

1. Commentary

1.1. Fibromyalgia is a disorder defined by "central sensitization".

Fibromyalgia is a diffuse non-focal chronic pain condition that occurs in 2–4% of the population, while the incidence among women aged 50–80 is even higher at 6–7% [1]. Fibromyalgia is thought to be stressor-induced, for example by a viral infection, physical or emotional stress, a traumatic accident, combat or surgery. Parallel phenomena are the chronic pain and fatigue found in syndromes such as Post Traumatic Stress Disorder (PTSD), "Gulf War Syndrome" and "Shell Shock". In this context, an allostatic load (stress) leads to a state of "distress" vs the healthy response of "eustress" [2,3]. A "wind-up" phenomenon in which repetitive activation of nociceptive nerves or C-fibers leads to augmented responses with additional input of nociceptive signals, associated early on with allodynia and hyperalgesia in fibromyalgia syndrome, results in neuronal plasticity and an altered pathologic state [4–6].

Specialists link this condition to a dysfunctional state of the nociceptive nervous system known as "central sensitization" and some investigators now use that term to describe fibromyalgia [7]. Normally, the nociceptive nervous system relays painful stimuli via peripheral sensory nerves to the CNS, and in time that pain is ultimately resolved by the down-modulation of both ascending and descending nociceptive signaling circuitry, allowing return to a healthy pain-free resting state. Some patients, however, fail to return to a pain-free state, even after the precipitating insult or stressor appears to have been resolved, causing clinicians to puzzle over why some patients get better and others don't. One possible explanation that is explored here, and tested in a companion paper in this issue, is a deficiency of testosterone in some individuals and not others.

The hallmarks of most peripheral inflammatory pain conditions are high WBC counts or local swelling, redness and soreness. In contrast, fibromyalgia patients have normal WBC counts, a normal erythrocyte sedimentation rate (which is usually elevated for inflammatory pain states in the clinic) and a lack of localized swelling or inflamed joints. Important early findings included the high levels of Substance P found in the cerebrospinal fluid of fibromyalgia patients [8,9], and the use of fMRI to evaluate altered patterns of cerebral activation and abnormally low pain thresholds when applying painful pressure to fibromyalgia patients compared with controls [10]. Substance P is of interest since it can amplify wind-up phenomena in chronic pain states and it has a pro-inflammatory effect on neutrophils, macrophages and lymphocytes [11]. Pathological features of chronic pain states within the nervous system include activated microglia within the spinal cord and activated sensory neuron-affiliated macrophages, as exemplified by cancer patients with chemotherapy-induced peripheral neuropathy [12]. Fibromyalgia is therefore best described as an inflamed nociceptive nervous system, distinctly different from various inflammatory states with high WBC counts in peripheral tissues.

1.2. Treatment guidelines for fibromyalgia patients

Current treatment guidelines for patients with fibromyalgia include patient education, exercise, cognitive behavioral therapy, CNS neurostimulatory therapies and pharmacologic therapies, which include NSAIDS, serotonin norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), tricyclic compounds, gabapentinoids, and the opioid antagonist naltrexone [7,13]. It is generally recognized, however, that these therapeutics can have suboptimal efficacy and/or adverse effects. NSAIDS are problematic when used for chronic conditions due to a significant risk for GI tract irritation; the side effects for anti-depressants such as SSRIs can be numerous and include risk of sexual dysfunction; and the gabapentinoids, including Pregabalin, have common side effects such as drowsiness, dizziness, fatigue, changes in libido and, for men, erectile dysfunction.

Opioids are sometimes prescribed but are now considered to be less effective for treating chronic pain than previously thought and their risk–benefit profile is poor due to serious adverse effects such as addiction, tolerance and opioid-induced hyperalgesia [7,14]. Opioids are also known to induce androgen deficiency (opioid-induced androgen deficiency, OPIAD) causing loss of libido and sexuality. Testosterone therapy in the presence of opioids has been used for treating the testosterone deficiency component in these patients, in combination with more aggressive opioid treatment for treating the pain component [15–18]. Testosterone therapy in the absence of exogenous opioids, however, has not been used for treating chronic pain in humans.

For the preliminary study described by White et al., elsewhere in this issue, the hypothesis was tested that testosterone therapy could be used to treat the chronic pain and fatigue of fibromyalgia patients without the well known side effects of currently prescribed pharmacologic agents. The rationale for using testosterone therapy resides in the combination of knowledge from diverse fields including reproductive endocrinology related to the gonadal steroid hormones, nociception, neuroendocrinology and reproductive immunology.

1.3. Preclinical and human studies causally link testosterone and pain

1.3.1. Gonadal steroid hormones and sexual dimorphisms

The function of androgens and their receptors, along with the knowledge that androgen receptors have been found and mapped out in the rodent brain, is associated with sexual differentiation during fetal development and reproductive behavior [19,20]. The relationship between testosterone and pain threshold has been investigated in animals [21–24], but the prevailing view has been that sex steroid hormones are involved early in the life of an animal to organize pain circuitry differentially by gender, resulting in the sexual dimorphisms observed for pain processing in adult males vs females [25]. No one has previously extended this concept further to consider whether exogenous sex steroid hormones, and testosterone in particular, can be used therapeutically to dampen pain in adult humans with low serum levels of testosterone and an inflamed nociceptive nervous system, even though serum free testosterone concentrations have been shown to be significantly decreased in premenopausal fibromyalgia patients relative to healthy volunteers [26].

1.3.2. Initial evidence of a role for testosterone in nociception

The discovery of aromatase-positive cells in the dorsal horn of the quail spinal cord [27] points to a role for testosterone in the regulation of pain threshold in adults. It is the dorsal horn where initial processing of pain sensation occurs (sensory neurons from the periphery synapse with CNS nociceptive relay neurons) and where transmission of nociceptive information to the thalamus and cerebral cortex via the anterolateral spinothalamic tract originates. Consistent with this, aromatase knockout (ArKO) mice unable to convert testosterone to 17β-estradiol have been shown to display increased nociceptive behaviors (decreased pain thresholds) upon challenge [28]. Thus, any testosterone/aromatase-dependent estrogen-mediated transcription of opiates, which has been shown to occur in the spinal and medullary dorsal horn [29–32], will not take place.

1.3.3. The inverse relationship between gonadal steroid hormones and inflammation

The concept that there is an inverse correlation between gonadal steroid hormones (estrogens, progestins and androgens) and inflammation, however, is well documented but underappreciated. First, at puberty, gonadal steroid hormone serum levels surge when the thymus correspondingly undergoes "involution", in which there is decreased thymic cellularity, decreased thymic cell development, and decreased thymic cell output to the periphery. Second, during pregnancy, an acute surge in gonadal steroid hormone serum levels results in further thymic involution, greatly decreased numbers of peripheral thymocytes